REMARKS

35 U.S.C. § 103(a) (Obviousness)

Claims 1, 4, 5, 7-11, 13-15, 17, 18, 20-21, 24-26, 28-31, 34-35, 38-40, 42, 43, and 46-50 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,403,091 to Lederman et al. ("Lederman") in view of U.S. Patent No. 5,597,563 to Beschorner et al. ("Beshorner") and U.S. Patent No. 6,056,956 to Cobbold et al. ("Cobbold") and in further view of U.S. Patent No. 4,959,302 to Cornaby et al. ("Cornaby"), for the reasons stated in the Office Action.

Applicants respectfully traverse this rejection, for the reason that no combination of the cited references would have given the skilled artisan guidance to induce T cell non-responsiveness to an allogeneic or xenogeneic donor tissue or organ in a human recipient comprising administering (a) a donor cell and (b) an anti-human gp39 antibody, or human soluble CD40 molecule in a five to eight day period prior to transplantation. Administration of anti-CD40 tolerizing agents within a five to eight day period prior to graft transplantation is not taught or suggested by any combination of the above-cited references.

Lederman describes antibodies to a T-cell antigen (5c8) which inhibit T-cell activation of B-cells. Lederman does not teach or suggest any method or time frame for administration of tolerizing agents prior to transplantation; therefore, Lederman does not make obvious the treatment or time frames of the methods of the claims.

Beschorner teaches induction of antigen-specific tolerance by administration of Antigen Presenting Cells (APCs). The Examiner cites Beschorner as teaching a 7 to 28 day administration of an immunosuppressive agent prior to administration of APCs. Office Action at 2. Applicants respectfully fail to see how administration of an *immunosuppressive agent* (in Beschorner, cyclosporine) relative to administration of a *tolerizing agent* (tolerogenic APCs) guides the skilled artisan in administration of a *tolerizing agent* (in the instant application, donor cells plus a CD40-L inhibitor, which are roughly equivalent to the immunosuppressive agent *and* the tolerizing agent of Beschorner) relative to administration of a *tissue graft*. Beschorner does not teach administration of tolerizing agents in any time frame relative to when the actual donor organ or tissue is transplanted. Therefore, Beschorner cannot make obvious the five to eight day treatment period of

the claims, and Beschorner in combination with Lederman fails to make obvious the methods of the claims.

Cobbold, similar to Beschorner, teaches tolerance to an antigen by administration of immunosuppressive antibodies prior to administration of either additional immunosuppressive antibodies or antigen to be tolerized to. The Examiner cites Cobbold as teaching a 1 to 7 day treatment of anti-T-cell antibodies prior to antigen exposure. Office Action at 2. Applicants respectfully point out to the Examiner that the paragraph cited by the Examiner (Cobbold, column 4, paragraph 3) gives a 1 to 7 day administration of T-cell-depleting antibodies prior to administration of non-T-cell-depleting antibodies. This paragraph does not teach a 1 to 7 day period for administration of antibodies relative to administration of antigen. But crucially, Cobbold, like Beschorner, does not suggest any time frame for administration of tolerizing antibodies and/or antigen *relative to time of transplant*. One of skill in the art, seeking to develop a method for preventing transplant rejection, could look to Cobbold or Beschorner for time frames for applying immunosuppressive agents relative to administration of the antigen to be tolerized against. But the same artisan would find no teachings for administration of immunosuppressive agents *and* tolerogenic antigen *relative to when the transplant is grafted*. Therefore, Cobbold in combination with Lederman and Beschorner does not teach the methods of the claims.

The Examiner cites Cornaby as teaching measurement of IL-2 or IL-2 receptor levels as an indicator that graft rejection is 2 to 8 days away. Office Action at 2. Applicants reiterate that this does not teach administration of tolerizing agents in any time frame relative to when the actual donor organ or tissue is transplanted; rather, Cornaby teaches measuring for impending rejection *following* graft transplant. This in no way provides guidance as to treatment regimes for tolerization *prior to* transplant. Therefore Cornaby cannot teach or suggest the methods of the claims.

Under no combination of Lederman, Beschorner, Cobbold, or Cornaby may be found teaching, suggestion, or motivation to administer gp39 antibody and donor cells from 5 to 8 days prior to the transplantation of allogeneic or xenogeneic donor tissues or organs. Therefore, the combination of these references fails to make obvious the claimed methods.

The Examiner contends that the five to eight day administration of tolerizing agents "appears well within the variable of an immunosuppressive regimen that achieved a recognized result of inhibiting or preventing graft rejection[.]" Office Action at 3. However, the Examiner does not provide a single immunosuppressive regimen for administration of tolerizing antibodies and antigen relative to transplant of donor tissues, let alone a treatment regimen that results in inhibiting or preventing transplant rejection. The Examiner further states that "The ordinary artisan provided immunosuppression prior, during, and after transplanting grafts of interest, including encompassing the newly amended regimen." Office Action at 3. Applicants respectfully submit that the Examiner has not provided evidence in support of this statement. In particular, no evidence has been provided that encompasses the regimen as set forth in the claims. Nor does "monitoring impending rejection" have any relation to the administration of the tolerizing regimen of the claims prior to transplant of donor tissue. Monitoring impending rejection takes place following transplantation, not before. Therefore no suggestion for administration prior to transplantation can be afforded by indications of treatment that rely on measurements taken after transplantation. Office Action at 3.

The time frame for administration of the tolerizing agents of the claims represents a significant difference in the method of tolerizing transplant recipients, a time frame which is in no way provided in the cited references. Prior to the disclosure of the instant invention, one of skill in the art attempting to tolerize an individual using an immunosuppressive agent would lack guidance as to the critical time frame and sequence for applying donor cells and gp39 antibodies as an immunosuppressive agent, relative to transplantation of the donor tissue, in order to achieve success. Using the methods of the invention as claimed, such a skilled artisan now has the tools in hand to properly tolerize a patient in need of an organ transplant using the gp39 antibodies of the invention.

In contrast to the Examiner's assertions, neither Beschorner nor Cobbold teach administration of antigen and/or antigen-expressing APCs in a five to eight day period prior to transplantation. Office Action at 3. Therefore, no combination of the above-cited references teaches or suggests the claimed methods. The cited references do not teach or suggest each and every element of the claimed invention; therefore, a *prima facie* case of obviousness has not been made.

For the reasons discussed above, the applicants submit that the present claims satisfy the requirements of 35 U.S.C. § 103(a), and request that the rejection of claims under § 103(a) be withdrawn.

Judicially created doctrine of obviousness-type double patenting

Claims 1, 4, 7-11, 13-15, 17, 20-21, 24-26, 28-31, 34-35, 38-40, 42-43 and 46-50 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 5,683,693, claims 1-34 of U.S. Patent No. 5,902,585, and claims 1-7 of U.S. Patent No. 6,375,950, and further in view of Beschorner, Cobbold, and Cornaby.

The Examiner's reasons for rejection, and therefore the Applicants' response, are essentially as described above.

The claimed methods of this application are patentably distinct over the claims of the above-identified patents. The claims identified above do not claim a method for inducing T cell non-responsiveness to a donor antigen by administering the tolerizing agents of the invention *from five to eight days prior to transplantation* of the tissue or organ to be transplanted. Administration of tolerizing agents within a five to eight day period prior to transplantation is not claimed in the above patents and is not obvious in view of these claims and the prior art. There is no teaching or suggestion of the five to eight day time period, in any combination of the above-patented claims with Beschorner, Cobbold, and Cornaby.

The Examiner has provided no evidence of a treatment regimen that the parameters of the claimed methods would fall within, including the claims of the above patents. Nor has the Examiner presented evidence that any methods resembling the claimed treatment methods are "well known and practiced by the ordinary artisan" for preventing graft rejection. Office Action at 4. Therefore, Applicants request that the rejection of the claims of the instant invention under the judicially created doctrine of obviousness-type double patenting be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing remarks. If any points remain in issue, Applicants hereby request an interview with the Examiner to further prosecution of this application.

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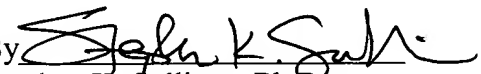
Respectfully submitted,

By 

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